Original Article

Intrauterine Levobupivacaine Instillation for Pain Control in Women Undergoing Diagnostic Hysteroscopy

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Abstract

Objectives: Many women experience pain and discomfort after hysteroscopic procedure. Pain and discomfort after hysteroscopic procedures can be explained by the cervical dilatation, intrauterine manipulation, and/or hydrodistension. This study designed to evaluate the efficacy of intrauterine levobupivacaine instillation for pain control in women undergoing diagnostic hysteroscopy.

Materials and Methods: One hundred and twenty (120) women scheduled for diagnostic hysteroscopy and endometrial biopsy due to uterine bleeding were included in this study and randomized either to levobupivacaine group or controls. At the end of hysteroscopy, 5 mL of 0.5% levobupivacaine was instilled intrauterine in levobupivacaine group, while 5 mL of 0.9% saline was instilled intrauterine in controls. Participants were kept in the hospital for 12 h after diagnostic hysteroscopy to detect the postoperative (PO) pain intensity using visual analog scale (VAS), and PO required analgesics.

Results: The VAS was significantly lower in levobupivacaine group compared to controls 3 h. PO (1.31 ± 1.02 vs. 1.62 ± 0.76, respectively), (P = 0.01), 6 h. PO (0.81 ± 1.24 vs. 1.53 ± 0.88, respectively), (P = 0.004), and 9 h. PO (0.55 ± 1.25 vs. 1.12 ± 0.95, respectively), (P = 0.01). The total PO required analgesics were significantly lower in levobupivacaine group compared to controls (P = 0.005).

Conclusion: The intrauterine levobupivacaine instillation was simple, and effective for pain relief after diagnostic hysteroscopy, it significantly decreased pain score assessed by VAS at 3, 6, and 9 h., PO, and it significantly decreased PO required analgesics.

Keywords: Diagnostic, hysteroscopy, intrauterine, levobupivacaine, pain

Introduction

Hysteroscopy is the gold standard for uterine cavity evaluation in many gynecological disorders including uterine bleeding (peri-menopausal and postmenopausal bleeding), and infertility.[1]

Many women experience some degree of pain and discomfort after hysteroscopic procedure.[2] Pain and discomfort after hysteroscopic procedures can be explained by the cervical dilatation during hysteroscopy, intrauterine manipulation, and/or hydro-distension.[2]

Postoperative (PO) pain control is crucial for both patient's satisfaction, and early PO discharge.[3]

Narcotics and nonsteroidal anti-inflammatory (NSAIDs) are the commonly used PO analgesics.[4] The disadvantages of narcotics include drowsiness, vomiting, and respiratory depression, while the disadvantages of NSAIDs include gastrointestinal upset and/or vomiting.[4]

Local blockers give satisfactory pain control without drowsiness, respiratory depression and/or vomiting.[3,4]

The efficacy of intrauterine lidocaine instillation for pain control after endometrial biopsies has been demonstrated in previous studies.[5,6]

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Intrauterine instillation of topical anesthetic is an easy, painless, and promising procedure for adequate PO analgesia after minor gynecological surgeries.[2]

Bupivacaine is a long-acting local anesthetic, it has a relatively delayed onset and longer duration of action than other local anesthetics.[2]

Therefore, the current randomized double-blinded study was designed to evaluate the efficacy of intrauterine levobupivacaine instillation for pain control in women undergoing diagnostic hysteroscopy.

Materials and Methods

This randomized double-blinded study was conducted from May 2019 to May 2020, after approval of the study by the Ethical Committee of the Obstetrics and Gynecology Department (approval number GY_0604_19).

One hundred and twenty women scheduled for diagnostic hysteroscopy and endometrial biopsy due to uterine bleeding (peri-menopausal or postmenopausal bleeding) were included in this study after informed consents in accordance with the Declaration of Helsinki.

Inclusion criteria include sexually active women ≥40-year-old presented with uterine bleeding either perimenopausal or postmenopausal bleeding, endometrial thickness >4 mm by transvaginal ultrasound (TVS), normal bleeding, and clotting times, normal activated partial thromboplastin time, and platelets count.[1]

Participants were subjected to thorough history, examination, speculum examination to exclude any cervical pathology or lesion, and Pap smear, followed by TVS by sonographer, blinded to participants' clinical data to evaluate the myometrium, endometrium, and any irregularities or distortion of endometrial cavity.

Unmarried women, women with the American Society of Anesthesiologists Class >II, endometrial thickness ≤4 mm, acute cervicitis and/or abnormal Pap smear, profuse uterine bleeding, known allergy to levobupivacaine, abnormal liver functions, endocrine disorders, pregnant, received hormonal therapy during last 6 months, cervical stenosis, or who were unable to score their pain on the visual analog scale (VAS) were excluded from the study.

After the preoperative laboratory investigations which were done according to hospital protocol and anesthesia consultation, eligible participants were randomally assigned using computer-generated randomization tables to either levobupivacaine group (60 women) or controls (60 women).

Diagnostic hysteroscopies were done following hospital protocol under general anesthesia using Bettocchi 5 mm, 30° hysteroscopy (Karl Storz, Germany), and normal saline as distension media. During hysteroscopies, the uterine cavity and endometrium were thoroughly evaluated (from the cervix to uterine fundus and both cornua), and any abnormal findings (i.e., polyps, myomas, septa, adhesions) were reported.

At the end of hysteroscopic procedures, endometrial biopsies were taken from all participants for histological examination, followed by intrauterine instillation of 5 mL of 0.5% levobupivacaine (Abbott, Republic of Ireland) in levobupivacaine group, while 5 mL of 0.9% saline was instilled intrauterine in controls.[2]

Participants were kept in the hospital for 12 h after diagnostic hysteroscopy (as per hospital protocol), and they were followed postoperatively by a medical team blinded to the intrauterine instilled medications (double-blinded) to record the participants' vital data, PO pain intensity using VAS (0 means lowest score: no pain, while 10 means highest score: unbearable pain), and PO required analgesics. Collected data were statistically analyzed to evaluate the efficacy of intrauterine levobupivacaine instillation for pain control in women undergoing diagnostic hysteroscopy.

Sample size justification

The required sample size was calculated from previous studies[1,2] and using G Power software version 3.1.9.7 for sample size calculation, setting α -error probability at 0.05, power (1-β error probability) at 0.95%, and effective sample size (w) at 0.5. An effective sample s110 women were needed to produce statistically acceptable figure.

Statistical analysis

Collected data were statistically analyzed using Statistical Package for Social Sciences (SPSS): computer software version 20 (Chicago, IL, USA). Numerical variables were presented as mean and standard deviation, while categorical variables were presented as number (n) and percentage (%). Chi-square test (x^2), and Student's *t*-test were used for analysis of qualitative, and quantitative variables, respectively.

Results

One hundred and twenty) women scheduled for diagnostic hysteroscopy and endometrial biopsy due to uterine bleeding were included in this study and randomized either to levobupivacaine group (60 women) or controls (60 women). At the end of diagnostic hysteroscopy, 5 mL of 0.5% levobupivacaine was instilled intrauterine in levobupivacaine group, while 5 mL of 0.9% saline was instilled intrauterine in controls to evaluate the efficacy of intrauterine levobupivacaine instillation for pain control in women undergoing diagnostic hysteroscopy.

The levobupivacaine group and controls were matched with no significant difference regarding, mean age (44.6 ± 7.9 years vs. 47.8 ± 9.2, respectively, P = 0.8), parity (3.2 ± 2.4 vs. 2.5 ± 3.6, respectively, P = 0.9), and body mass index (BMI), (26.6 ± 3.5 Kg/m^2 vs. 25.8 ± 2.9, respectively, P = 0.07) Table 1.

There was no significant difference between levobupivacaine group, and controls regarding the indications of hysteroscopy; postmenopausal bleeding (20% [12/60] vs. 23.3% [14/60], respectively, P = 0.7), heavy menstrual bleeding (56.2% [27/48] vs. 45.6% [21/46], respectively, P = 0.4), metrorrhagia (29.2% [14/48] vs. 28.3% [13/46], respectively, P = 0.8), and polymenorrhea (14.6% [7/48] vs. 26.1 [12/46], respectively, P = 0.2). In addition, the was no significant difference between levobupivacaine group and controls regarding, endometrial thickness before hysteroscopy (6.7 ± 2.4 mm vs. 7.1 ± 4.3, respectively, P = 0.9), and duration of the diagnostic hysteroscopy (7.5 ± 0.9 min. vs. 8.3 ± 1.5, respectively, P = 0.9) [Table 1].

There was no significant difference between the two-studied groups regarding, the heart rate, mean arterial blood pressure (MAP), and pulsed oxygen saturation (SPO_2) at awakening (P = 0.1, 0.1, and 0.9, respectively), at 3 h. PO (P = 0.4, 0.7, and 1.0, respectively), or at 6 h. PO (P = 0.2, 0.9, and 0.9, respectively). In addition, the was no significant difference between the two-studied groups regarding, the heart rate, MAP, and SPO_2 at 9 h. PO (P = 0.9, 0.2, and 0.8, respectively), or at 12 h. PO (P = 0.2, 0.2, and 0.9, respectively) Table 2.

The VAS was significantly lower in levobupivacaine group compared to controls 3 h. PO (1.31 ± 1.02 vs. 1.62 ± 0.76, respectively), (P = 0.01, [95% CI: −0.64, −0.3, 0.017]), 6 h. PO (0.81 ± 1.24 vs. 1.53 ± 0.88, respectively), (P = 0.004, [95% CI: −1.11, −0.72, −0.33]), and 9 h. PO (0.55 ± 1.25 vs. 1.12 ± 0.95, respectively), (P = 0.01, [95% CI: −0.97, 0.57, −0.17]) Table 3.

While there was no significant difference between the two-studied groups regarding the VAS at awakening (P = 0.2) or 12 h. PO (P = 1.0) Table 3.

Regarding the PO required analgesics; one woman (1.66%) in levobupivacaine group required oral paracetamol compared to 4 controls (6.7%), (P = 0.1), while no NSAIDs or narcotics (0% and 0%, respectively) were required in levobupivacaine group compared to 6.7% (4/60) and 5% (3/60), respectively in controls (P = 0.01 and 0.03, respectively). The total PO required analgesics were significantly lower in levobupivacaine group compared to controls (1.66% [1/60] vs. 18.3% (11/60), respectively), (P = 0.005) Table 4.

There was no significant difference between the two-studied groups regarding the histological results of endometrial biopsies [Table 4].

Discussion

The uterus and uterine cervix are richly innervated. The perception of pain from the uterus and uterine cervix pass through the parasympathetic nerves (S2, S3, and S4), and sympathetic nerves.[2,7]

Although the Pipelle endometrial sampling is an accurate, cost-effective outpatient procedure, avoids general anesthesia with 100% accuracy in diagnosing endometrial hyperplasia, and carcinoma. It had low sensitivity (60%) in diagnosing endometrial polyps.[8] In addition, Abdelazim *et al*., found the endometrial brush cytology an accurate, outpatient procedure, avoids general anesthesia and could be used as a complementary diagnostic tool when hysteroscopic biopsies are not available.[9]

Based on the low sensitivity (60%) of Pipelle endometrial sampling in diagnosing endometrial polyp and availability of

Table 1: Demographic data, indications, and duration of hysteroscopy in the two-studied groups

Variables	Levobupivacaine group (60 women)	Controls (60 women)	*P* (95% CI)
Age (years)	44.6±7.9	47.8±9.2	0.8 (−6.3, −3.2, 0.09)
Parity	3.2±2.4	2.5±3.6	0.9 (−0.41, −0.7, 1.8)
BMI (kg/m^2)	26.6±3.5	25.8±2.9	0.07 (−0.37, 0.8, 1.97)
Indications of hysteroscopy (%)			
Postmenopausal bleeding	12 (20)	14 (23.3)	0.7
Peri-menopausal bleeding	48 (80)	46 (76.7)	0.8
HMB	27 (56.2)	21 (45.6)	0.4
Metrorrhagia	14 (29.2)	13 (28.3)	0.8
Polymenorrhea	7 (14.6)	12 (26.1)	0.2
Endometrial thickness (mm)	6.7±2.4	7.1±4.3	0.9 (−1.7, 0.4, 0.9)
Duration of hysteroscopy (min)	7.5±0.9	8.3±1.5	0.9 (−1.25, −0.8, −0.35)

Chi-square test (χ^2) used for statistical analysis when data presented as number and percentage (%), Data presented as mean±SD and number and percentage (%), Metrorrhagia means bleeding in between regular cycles, Polymenorrhea: Frequent cycles within <21 days. Student *t*-test used for statistical analysis when data presented as mean±SD. BMI: Body mass index, HMB: Heavy menstrual bleeding, SD: Standard deviation

Table 2: Postoperative vital data (heart rate and arterial blood pressure), and pulsed oxygen saturation of the two-studied groups

Variables	Levobupivacaine (60 women)	Controls (60 women)	*P* (95% CI)
At awakening			
HR	86.8±3.75	73.2±3.23	0.1 (12.3, 13.6, 14.87)
MAP	73.5±4.96	72.1±4.21	0.1 (−0.26, 1.4, 3.06)
SPO_2	98.5±0.69	99.1±1.11	0.9 (−0.94, −0.6, −0.26)
At 3 h PO			
HR	86.9±3.2	74.4±3.1	0.4 (11.36, 12.5, 13.6)
MAP	70.2±2.6	69.6±2.8	0.7 (−0.37, 0.6, 1.57)
SPO_2	98.5±0.69	98.9±1.3	1.0 (−0.78, −0.4, −0.02)
At 6 h PO			
HR	85.9±5.6	83.5±5.1	0.2 (0.46, 2.4, 4.34)
MAP	76.9±3.03	73.7±3.6	0.9 (1.99, 3.2, 4.41)
SPO_2	98.5±0.94	97±1.25	0.9 (1.10, 1.5, 1.89)
At 9 h PO			
HR	84.8±3.4	83.5±4.11	0.9 (−0.07, 1.3, 2.67)
MAP	75.6±3.4	69.6±3.1	0.2 (4.8, 6, 7.178)
SPO_2	98.5±0.69	97.5±0.81	0.8 (0.73, 1, 1.27)
At 12 h PO			
HR	85.6±4.1	84.7±3.7	0.2 (−0.51, 0.9, 2.31)
MAP	77.8±4.3	72.9±3.9	0.2 (3.42, 4.9, 6.38)
SPO_2	98.5±2.67	97.6±3.6	0.9 (−0.25, 0.9, 2.05)

Data presented as mean±SD, Student *t*-test used for statistical analysis. PO: Postoperative, HR: Heart rate, MAP: Mean arterial blood pressure, SPO_2: Pulsed oxygen saturation, SD: Standard deviation

Table 3: Postoperative Visual Analogue Scale of the two-studied groups

VAS	Levobupivacaine group (60 women)	Controls (60 women)	*P* (95% CI)
At awakening	1.46±1.35	2.85±1.25	0.2 (−1.86, −1.39, −0.92)
At 3 h PO	1.31±1.02	1.62±0.76	0.01* (−0.64, −0.3, 0.017)
At 6 h PO	0.81±1.24	1.53±0.88	0.004* (−1.11, −0.72, −0.33)
At 9 h PO	0.55±1.25	1.12±0.95	0.01* (−0.97, 0.57, −0.17)
At 12 h PO	0.35±0.05	1.95±1.35	1.0 (−1.95, −1.6, −1.3)

*Significant difference, Data presented as mean±SD, Student *t*-test used for statistical analysis. CI: Confidence interval, PO: Postoperative, VAS: Visual Analogue Scale

Table 4: Postoperative required analgesics, and results of endometrial biopsies in the two-studied groups

Variables	Levobupivacaine group (60 women) (%)	Controls (60 women) (%)	*P*
Total PO need for analgesics	1 (1.66)	11 (18.3)	0.005*
Narcotics	0	3 (5)	0.03*
NSAIDs	0	4 (6.7)	0.01*
Paracetamol	1 (1.66)	4 (6.7)	0.1
Histological results of endometrial biopsies			
Proliferative endometrium	27 (45)	25 (41.7)	0.8
Secretary endometrium	15 (25)	12 (20)	0.6
Endometrial polyp	7 (11.7)	9 (15)	0.6
Endometrial hyperplasia	5 (8.3)	8 (13.3)	0.4
Chronic endometritis	3 (5)	4 (6.7)	0.7
Atrophic endometrium	3 (5)	2 (3.3)	0.66

*Significant difference, Chi-square test (χ^2) was used for statistical analysis, Data presented as number and percentage (%). PO: Postoperative, NSAIDs: Non-steroidal anti-inflammatory drugs

hysteroscopy, our hospital adopted endometrial sampling using Pipelle or brush in outpatients setting only in high-risk women for anesthesia (i.e., old women with multiple medical disorders).

Many women experience some degree of pain and discomfort after hysteroscopic procedure.[2] Pain after hysteroscopic procedures can be explained by the cervical dilatation during

hysteroscopy, intrauterine manipulation, hydro-distension, and/or endometrial biopsy.[2]

The para-cervical block can decrease pain of cervical origin.[10] However, it was ineffective in decreasing pain originated from the uterine corpus, and it was associated with risks of bradycardia, hypotension, and respiratory arrest.[11]

On the other hand, the intrauterine local anesthetic instillation may decrease pain arising from the uterine body.[2] Therefore, one hundred and twenty (120) women scheduled for diagnostic hysteroscopy, and endometrial biopsy due to uterine bleeding according to hospital protocol were randomized in this study either to levobupivacaine group (60 women) or controls (60 women). At the end of diagnostic hysteroscopy, 5 mL of 0.5% levobupivacaine was instilled intrauterine in levobupivacaine group, while 5 mL of 0.9% saline was instilled intrauterine in controls to evaluate the efficacy of intrauterine levobupivacaine instillation for pain control in women undergoing diagnostic hysteroscopy.

There was no significant difference between the two-studied groups regarding, the mean age (P = 0.8), parity (P = 0.9), BMI (P = 0.07), endometrial thickness before hysteroscopy (P = 0.9), and duration of diagnostic hysteroscopy (P = 0.9).

Although Lau *et al*., randomized double-blinded study found the intrauterine instillation of 2% lignocaine (5 mL) neither reduced pain nor prevented vasovagal reaction during outpatient hysteroscopy.[12]

The VAS in this study was significantly lower in levobupivacaine group compared to controls 3 h. PO (1.31 ± 1.02 vs. 1.62 ± 0.76, respectively), (P = 0.01), 6 h. PO (0.81 ± 1.24 vs. 1.53 ± 0.88, respectively), (P = 0.004), and 9 h. PO (0.55 ± 1.25 vs. 1.12 ± 0.95, respectively), (P = 0.01).

Hui *et al*., randomized, double-blind, placebo-controlled trial found the intrauterine instillation of lignocaine reduced pain during endometrial sampling.[13]

Benchahong *et al*., also found the intrauterine lidocaine instillation was an effective analgesia during endometrial sampling and curettage.[14]

Moreover, Guler *et al*. found the intrauterine lidocaine decreases pain during Pipelle endometrial sampling more efficiently compared to paracervical block.[15]

Mizrak *et al*., also found the intrauterine levobupivacaine or bupivacaine was effective in pain relief following endometrial biopsy and curettage.[16]

Bhatia *et al*., a pilot study found the intrauterine instillation of dilute bupivacaine (125 mg) was safe, feasible, and effective for PO pain relief after endometrial balloon ablation procedure.[17]

In this study, the total PO required analgesics were significantly lower in levobupivacaine group compared to controls (1.66% vs. 18.3%, respectively), (P = 0.005).

Mercier and Zerden, systematic review (23 articles included) found the intrauterine local anesthesia can significantly reduce and relief pain after several gynecologic procedures including endometrial biopsy, endometrial curettage, and hysteroscopy.[18]

Kosus *et al*., found the intrauterine instillation of levobupivacaine or lidocaine causes pain relief during endometrial biopsy, and they recommended further studies to determine the optimal concentration and volume of local anesthetic needed.[2]

The Bupivacaine was used in this study as local anesthetic because it is a long-acting local anesthetic, it has a relatively delayed onset and longer duration of action than other local anesthetics.[2] A 5 mL of either 0.5% levobupivacaine (levobupivacaine group) or 0.9% saline (controls) were instilled intrauterine in this study, because the intrauterine instillation of 5 mL of local anesthetic was recommended previously,[2] and 5 mL volume of local anesthetic is sufficient to fill the uterine cavity, without tubal overspill.[2]

This study found that the VAS was significantly lower in levobupivacaine group compared to controls 3, 6, and 9 h., after diagnostic hysteroscopy, and the total PO required analgesics were significantly lower in levobupivacaine group compared to controls.

Women refused to participate, small sample size, and failure to assess the patients' satisfaction were the limitations faced during this study. Further studies are needed to confirm the efficacy of intrauterine local anesthetics for pain relief in women undergoing intrauterine procedures.

Conclusion

The intrauterine levobupivacaine instillation was simple, and effective for pain relief after diagnostic hysteroscopy, it significantly decreased pain score assessed by VAS at 3, 6, and 9 h., PO, and it significantly decreased PO required analgesics.

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Conflicts of interest

There are no conflicts of interest.

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